REMARKS

The August 19, 2003 Official Action and the reference cited therein have been carefully considered. In view of the amendment submitted herewith and these remarks, favorable reconsideration and allowance of this Application are respectfully requested.

In the Official Action, claims 5-11, and 14-17 are indicated as allowable if rewritten in independent form.

Additionally, at page 2 of the Official Action, the Examiner rejects claims 1-4, 12, 13, and 18 under 35 U.S.C. §102(b) as allegedly being anticipated by Merianos et al. (U.S. Patent No. 5,209,922). This is the sole ground of the rejection set forth in the August 19, 2003 Official Action.

In accordance with the present amendment, claims 1-4 are canceled; claims 5, 12, and 15-18 are amended; and new claims 19-26 are added. Accordingly claims 5-26 are currently pending in the present Application.

Claims 5 and 12 have been rewritten in independent form incorporating all the limitations recited in canceled claims 1 and 3, from which they were dependent. Additionally, claim 12 is further amended to recite that the composition of matter is formed in an aqueous medium and that the supramolecular complex has a particle size less than 500 nm. Support for these amendments can be found at page 43 of the specification, wherein sodium phosphate buffer (SPB) or TRIS-buffer was used in Examples 10-14 to form a complex of the type encompassed by claim 12, and at page 30, lines 13-18 of the specification, where it is disclosed that the preferred size of the complex is less than 500 nm.

Claims 15-18 have been amended to depend from claim 5.

New claims 19-20 incorporate all the limitations recited in canceled claim 4 but depend from claims 5 and 12, respectively.

New claims 21-22 are further directed to compositions as claimed in claim 12 wherein the particle size is less than 200 or 100 nm. Again, support for these recitations can be found at page 30, lines 13-18 of the specification.

New claims 23-26 incorporate all the limitations recited in original claims 15-18 but depend from claim 12.

In summary, the amended claims 5, 12, and 15-18 and the newly added claims 19-25 are directed to particular embodiments of the present invention. No new matter is introduced by the present claim amendment, entry of which is respectfully requested.

In light of the foregoing amendment and the following remarks the above-noted rejection of claims 1-4, 12, 13, and 18 under 35 U.S.C. §102(b) based on Merianos et al. is respectfully traversed.

Amended Claim 5 And Its Dependent Claims (Claims 6-11 and 15-19) Are Allowable

As indicated in the present Official Action, original claims 5-11 and 14-17 are considered allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. By the present amendment, claim 5 is now amended to independent form incorporating all the limitations recited in canceled claims 1 and 3. Additionally, currently amended claims 15-18 and newly added claim 19 are dependent from claim 5 and drawn to particular embodiments of the present invention, as noted above. Thus, it is Applicants' belief that claim 5 and its dependent claims, claims 6-11, and 15-19, as they are presented hereinwith, are now in condition for allowance.

Amended Claim 12 And Its Dependent Claims (Claims 13-14 and 20-26) Are Patentably Distinguishable From Merianos et al.

It is the Examiner's position that Merianos et al. teach a block polymer comprising poly(vinyl lactam) units and quarternized amino alkyl acrylamide units, with the later being ionically bound to undecyclenic acid. The Examiner further asserts that claims 12 and 13 are anticipated by Merianos et al. This rejection is respectfully traversed for the following reasons.

In order to constitute evidence of lack of novelty under 35 U.S.C. §102(b), a prior art reference must identically disclose each and every element of the rejected claim. In re Bond, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990).

In the instant case, claim 12 has been amended to recite a composition comprising a therapeutic or diagnostic agent and a composition of matter forming a supramolecular complex in aqueous medium and comprising a block copolymer, having at least one nonionic, water soluble segment and at least one polycationic segment, and further comprising at least one charged surfactant having hydrophobic groups, the charge of said surfactant being opposite to the charge of the polycationic segment of said block copolymer. Claim 12 further recites that i) the composition forms a supramolecular complex in an aqueous medium (see Examples 10-14 at pages 42-44 of the specification, wherein sodium phosphate buffer (SPB) or TRIS-buffer is used); ii) the constituents of the complex are bound by interactions between the opposite charges and between surfactant hydrophobic groups (see page 3, lines 20-25 of the specification); and iii) the complex has a particle size less than 500 nm (see page 30, lines 13-18 of the specification). None of these three recitations is taught or suggested by Marianos et al.

It is noteworthy that the polymer complex of Marianos et al. is formed in methanol, an organic solvent, see Example 1 at column 4 of Marianos et al. That being the case no interactions between the surfactant hydrophobic groups would occur in the complexes of Marianos et al. because the methanol environment would inhibit such interactions. This lack of interaction between surfactant hydrophobic groups in an alcohol-containing media is evidenced by the study of Khandurina et al. in "Stability of Polycomplexes of Cross-Linked Polyelectrolytes with Surfactants in Aqueous Salt and Aqueous Organic Media", *Polymer Science* 1994;36(2):195,198, a copy of which is attached. In Khandurina et al., the authors investigated the stability of polymer-surfactant complexes (PSC) in aqueous salt and alcohol-containing media. Khandurina et al. teach that "the hydrophobic interaction between the aliphatic surfactant radicals contributes significantly to the stabilization of PSC in aqueous media". The authors found that "the weakening of hydrophobic contacts in the PSC species upon going from aqueous to aqueous organic media will facilitate the dissociation of the complex".

Moreover, "[t]he dissociation of PSC ... in an aqueous alcohol media is accompanied by a sharp increase in the degree of swelling *H* of the complexes (by one order of magnitude or even greater)." In summary, it is clear that the "interaction between surfactant hydrophobic groups", which is called for in amended claim 12, would not occur in the block copolymers described in Marianos et al., as they are prepared in a methanol medium.

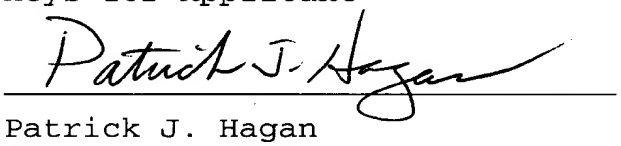
Further, as disclosed at page 30, lines 13-18 of the present specification, the compositions of the present invention normally form complexes of small size, preferably less than 500 nm, which is important because small particles can easily penetrate into tissues through even small capillaries and enter cells via endocytosis. Although it is stated in Example 1 of Marianos et al. that during the formation of the complex, "[t]he solution were heated to about 55°C and mixed for 2 hours to provide a hazy suspension of fine particles", it is noted that this suspension of fine particles was formed in methanol. Also in Example 1 of Marianos et al., it is stated that the mixture with fine particles was further evaporated to remove methanol and dried under vacuum. Accordingly, it is unlikely that these fine particles would survive such processing, and be still present in the final dry form of the complex. It should also be noted that a small particle size is not required for the end uses described in Marianos et al., i.e. powder, dust, moisturizing cream, foot cream, aerosol foot powder, aerosol powder, and dry powder stick.

In conclusion, Marianos et al. fails to disclose each and every element of claim 12. Therefore, the rejection of claim 12 under U.S.C. §102(b) based on Merianos et al. should be withdrawn and claim 12, as it is presently amended, should be allowed. Furthermore, inasmuch as claims 13-14, and new claims 20-26 are dependent from claim 12 and directed to particular embodiments of the composition recited in claim 12, these claims should also be allowed.

Conclusion

In view of the amendments and remarks presented herewith, it is respectfully urged that the objections and rejections set forth in the August 19, 2003 Official Action be withdrawn and that this application be passed to issue. In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any issues outstanding may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number given above.

Respectfully submitted,
DANN DORFMAN HERRELL and SKILLMAN, P.C.
Attorneys for Applicant

By 

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Enclosure:

- Khandurina et al. *Polymer Science* 1994;36(2):195,198

Polymer Science, Vol. 36, No. 2, 1994, pp. 195 - 199. Translated from Vysokomolekulyarnye Soedineniya, Vol. 36, No. 2, 1994, pp. 241 - 246.

Stability of Polycomplexes of Cross-Linked Polyelectrolytes with Surfactants in Aqueous Salt and Aqueous Organic Media[1]

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Abstract – The stability of polymer–surfactant complexes of cross-linked sodium polyacrylate with various cationic surfactants in aqueous salt and aqueous organic media was studied. The stability of such complexes at small concentrations of low-molecular-mass electrolyte is determined by the concentration of a molecular-disperse surfactant in the medium. At large electrolyte concentrations (of the order of 0.45 mol/l), the destruction of the polymer–surfactant complexes represents a cooperative process of detachment of the micellar clusters of the surfactant from segments of the oppositely-charged network. The introduction of an organic solvent (alcohol) in the system produces dissociation of the complexes, which is accompanied by a sharp increase in the swelling ability of polycomplex gels.

In recent years, the attention of researchers has been attracted to polymer–surfactant complexes (PSC) formed by the reaction of polyions with oppositely charged ions of micelle-forming surfactant. These compounds may be treated as polyelectrolytes, with surfactant ions acting as counterions. In a number of works these complexes were considered as a new class of amphiphilic polymeric substances, the structure and properties of which critically depend on the ratio of components [1 - 6]. The published data have demonstrated possible practical applications of these substances, for example, as efficient floculants. They can also be used in systems capable of extracting organic compounds of various nature dissolved or dispersed in water [1, 3, 7]. Obviously, the possibility and efficiency of the application of PSC directly depend on the stability of these compounds, that is, on the ability to dissociate in aqueous, aqueous salt, and aqueous organic media.

This work is devoted to studying the behavior and stability of PSC formed by a lightly cross-linked polyacrylic acid (*cl*-PAA) and typical surfactant cations, specifically, the alkyltrimethyl ammonium and alkylpyridinium cations. In what follows, we will use the abbreviation PSC(*cl*-PA–surfactant), with a polyanion and a surfactant cation indicated in parentheses.

EXPERIMENTAL

The *cl*-PAA gel was obtained by radical copolymerization of freshly distilled acrylic acid (AA) with *N,N*-methylenebisacrylamide (with a monomer mass ratio of 100 : 1) in a 10% aqueous solution. The reaction was initiated by ammonium persulfate and sodium metabisulfite (0.2% of the AA mass) and carried out for 1 day at 40°C. The *cl*-PAA gel was completely neutralized with NaOH. The samples of cross-linked sodium polyacrylate (*cl*-PA-Na) appeared as transparent homogeneous elastic monoliths. The concentration of COONa groups in an equilibrium-swollen, completely ionized *cl*-PA-Na sample was about 10^{-2} base-mol/l. The swollen samples had a cubic shape and a mass varying from 1 to 10 g.

The surface-active substances were dodecylpyridinium chloride (DPC), cetylpyridinium bromide (CPB), dodecyltrimethylammonium bromide (DTMAB), tetradecyltrimethylammonium bromide (TTMAB), and cetyltrimethylammonium bromide (CTMAB). All surfactants were purified by crystallization from an ethanol–acetone mixture (15 : 85). In addition, we also used cetylamine and undecylamine hydrochlorides. The concentrations of substances containing pyridinium groups (CPB and DPC) were determined spectrophotometrically, using the intensity of absorption at a wavelength of $\lambda = 259$ nm ($\varepsilon = 4100$). The measurements were carried out on a Hitachi 150-20 spectrophotometer.

RESULTS AND DISCUSSION

The PSC (*cl*-PA–surfactant) samples were obtained by placing a *cl*-PA-Na gel into an aqueous solution of the appropriate surfactant. The formation of the PSC (*cl*-PA–surfactant) samples was described in [8, 9]. The process appears as a frontal heterogeneous reaction, featuring the advance of a sharp interface from the periphery of the sample to its center. The interface separates an outer dense (low-water-swollen) PSC layer and a strongly swollen inner part of the intact gel, as

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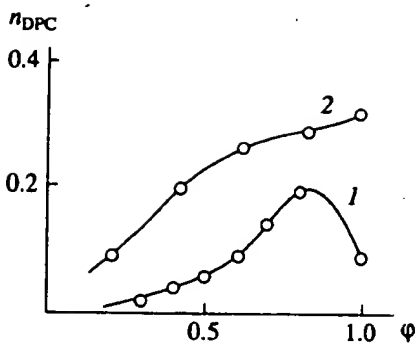


Fig. 2. Relative amount of DPC liberated from PSC (*cl*-PA–DP) into the surrounding solution vs. the volume fraction φ of (*1*) ethanol and (*2*) isopropanol; $m_{PSC(dry)} \approx 0.02$ g; $V_{sol} = 15$ ml; $T = 20°C$.

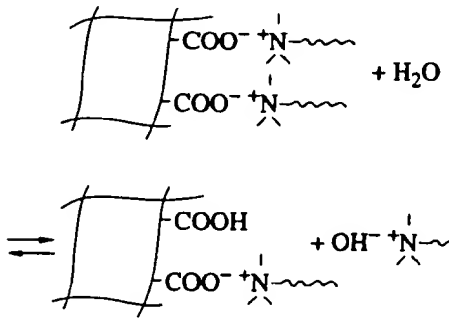
lamella thickness depending on the length of the aliphatic surfactant radical. The density of charge on the lamellae surface is apparently determined by the nature of the surfactant ionic group. Indeed, we have found that PSC formed by *cl*-PA-Na and by protonated fatty primary amines (cetyl and undecylamine) exhibits higher stability in NaCl solutions than do the PSC formed by quaternary alkylpyridinium and alkyltrimethylammonium cations. For example, PSC (*cl*-PAA–DP), PSC (*cl*-PA–DTMA), PSC (*cl*-PA–CP), and PSC (*cl*-PA–CTMA) decompose in 0.45 M NaCl, whereas PSC (*cl*-PA–cetylamine) and PSC (*cl*-PAA–undecylamine) remain stable up to $c_{NaCl} \approx 1.5$ mol/l. The high stability of the latter two complexes seems to be due to closer packing of the ionogenic groups on the lamellae surface as compared to the packing of more bulky quaternary pyridinium and trimethylammonium cations.

Therefore, when the CMC value of the free surfactant is higher than its concentration in solution, the stability of the polymer–surfactant complexes in aqueous salt media of low ionic strengths is determined by the concentration of dissolved surfactant. At high salt concentrations, when the CMC of surfactant is lower than its concentration in the solution, the PSC stability is no longer dependent on the surfactant concentration. Under these conditions, the micellar surfactant clusters act as partners in equilibrium with PSC [scheme (4)].

As was noted above, the hydrophobic interaction between the aliphatic surfactant radicals contributes significantly to the stabilization of PSC in aqueous media. It is, therefore, expected that the weakening of hydrophobic contacts in the PSC species upon going from aqueous to aqueous organic media will facilitate the dissociation of the complex. Indeed, we have found that the *cl*-PA-Na gel looses its ability to sorb the DPC cations from aqueous alcoholic solutions if the water contains ethanol or isopropanol at a concentration of 50 and 40 vol %, respectiv ly. We hav studied the stability of PSC (*cl*-PA–surfactant) in aqueous ethanol and aqueous isopropanol media. The samples of preliminarily prepared PSC (*cl*-PA–DP), PSC (*cl*-PA–DTMA), and PSC (*cl*-PA–CP) were placed into a relatively large volume of solution of a definite composition (which was greater by one order of magnitude than the polycomplex sample volume) and stored for several days at a definite temperature. The concentration of surfactant (DP and CP) ions in the aqueous alcohol solution was then determined spectrophotometrically.

Figure 2 shows the relative surfactant content ($n_{surfactant}$, the ratio of the amount of surfactant liberated into solution to the total surfactant in the initial polycomplex) in the solution around the polycomplex versus the aqueous alcohol mixture composition. It is clear that the amount of surfactant in the surrounding solution increases with increasing alcohol concentration. This indicates a decrease in the stability and a gradual dissociation of the complex. Note that the experiment was carried out in salt-free media, that is, under the conditions when the liberation of surfactant results from the hydrolysis of the salt bonds in PSC rather than from the screening of opposite charges.

Indeed, the immersion of PSC samples into aqueous alcohol mixtures produces an increase in pH (from 7 to 10), which indicates the occurrence of reaction (5).



(5)

The equilibrium of this reaction can be almost completely shifted to the right (i.e., the complex can be dissociated) by increasing the volume of the liquid surrounding the gel. In other words, the addition of an organic solvent to break the hydrophobic bonds transforms the system from the regime of cooperative multisite interaction between polyanionic fragments of the network and micellar clusters, to the state of ordinary interaction between a network polyanion and small surfactant conterions. Adding low-molecular-mass salt (NaCl) to the aqueous alcohol mixture will additionally destabilize PSC and lead eventually to their complete dissociation and liberation of surfactant ions into the surrounding solution.

The dissociation of PSC (*cl*-PA–surfactant) in an aqueous alcohol media is accompanied by a sharp increase in the degree of swelling *H* of the complexes (by one order of magnitude or even greater). Figure 3 shows the plots of *H* versus the alcohol (ethanol or isopropanol) content in the solution for PSC (*cl*-PA–DP) (curves *1* and *2*) and PSC (*cl*-PA–CP) (curves *3* and *4*) systems. The marked increase in the swelling can be naturally attributed to the destruction of surfactant micelles immobilized in the network polyelectrolyte,